IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:	Confirmation No.: 5927
Nicholas M. VALIANTE, Jr.	Examiner: Y. S. Chong
Application No.: 10/762,873	Group Art Unit: 1617
Filed: January 21, 2004	
For: USE OF TRYPTANTHRIN COMPOUNDS FOR IMMUNE POTENTIATION	

BRIEF ON APPEAL

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The rejection of claims 12-17 and 19 is hereby appealed. This Brief is filed in accordance with 37 C.F.R. § 41.37.

A Notice of Appeal was filed in the present application on 6 April 2009, along with a Pre-Appeal Brief Request for Review. A decision stating that there were still appealable issues with respect to the appealed claims 12-17 and 19 was mailed 3 August 2009. Thus, the due date for filing of a Brief was 3 September 2009. A petition for an extension of time of five (5) months until 3 February 2010 is enclosed along with the required fee.

Claims 12-17 and 19 are subject to this Appeal.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I. REAL PARTY IN INTEREST

The Real Party in Interest is the assignee herein, Novartis, A.G., having an address at Lichtstrasse 35, 4056 Basel, Switzerland.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their representatives and assignees are unaware of any proceedings related to, directly affecting or that would be directly affected by or have a bearing on the Board's decision in this case.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 22 claims pending in the application.

B. Current Status of Claims

1. Claims canceled: 23-31
2. Claims withdrawn from consideration but not canceled: 1-11, 18, 20-22
3. Claims pending: 1-22
4. Claims allowed: None
5. Claims rejected: 12-17, 19
6. Claims objected to: None

C. Claims on Appeal

The claims on appeal are claims 12-17 and 19.

IV. STATUS OF AMENDMENTS

No amendments to the claims were proposed after final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

There is one independent claim, claim 12, from which all remaining claims on appeal depend.

Claim 12 is directed towards an immunogenic pharmaceutical composition comprising an antigen and a 'tryptanthrin compound adjuvant' that acts as an adjuvant to promote antigenic response to the antigen in the composition. See specification at page 3, paragraph [014]. Claim 12 further provides that the tryptanthrin compound adjuvant is present in an amount effective to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant. See specification at page 5, paragraph [024]. A generic description of the claimed compositions is provided by the specification at, e.g., page 5, paragraph [024].

The various features of independent claim 12 are supported by the specification as indicated below:

1. An immunogenic pharmaceutical composition (page 10, paragraph [044]) comprising an antigen (page 3, paragraph [014]) and a tryptanthrin compound adjuvant (page 3, paragraph [014]) in an amount effective to provide an enhanced immune response to the antigen (page 5, paragraph [024]) relative to the response provided without the tryptanthrin compound adjuvant (page 9, paragraph [039]).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 12-17 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable for obviousness over Baker et al. (U.S. Patent 5,441,955) [hereinafter "Baker"] in view of Colston et al. (U.S. Patent 7,122,195) [hereinafter "Colston"].

VII. ARGUMENT

A. The combination of Baker in view of Colston fails to establish a *prima facie* case of obviousness

1. Brief Summary of Pertinent Disclosures of Baker and Colston

Baker discloses its tryptanthrin compounds are useful for controlling the growth of pathogenic mycobacteria. See Baker, col. 3, lines 16-23: "The present invention provides methods of inhibiting the growth of pathogenic mycobacteria in vitro and of treatment of pathogenic mycobacterial infections in vivo using indolo[2,1-b]quinazoline-6,12-dione compounds of the formula (I)." Baker's compounds are expressly stated to be useful to kill mycobacteria. See Baker, col. 1, lines 7-14: "The present invention relates to new indolo[2,1-b]quinazoline-6,12-dione derivatives which are useful in killing mycobacteria...."

Baker discloses that its compounds may be used alone or in combination with other agents used to treat pathogenic mycobacterial infections, exemplified by antibacterial agents such as isoniazid, rifampin, pyrazinamide, ethambutol, rifabutin, streptomycin, and ciprofloxacin. See Baker, col. 13, lines 36-44. Unit dosage formulations of Baker's compounds may contain "conventional nontoxic pharmaceutically acceptable carriers, *adjuvants*, and vehicles." See Baker, col. 12, lines 37-42 (emphasis added). The meaning of 'adjuvants' in the context of Baker's disclosed

formulations is further clarified at col. 13, lines 15-18, which states: "Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents." Thus, the 'adjuvants' disclosed by Baker are conventional pharmaceutical excipients.

Colston discloses vaccine compositions comprising a live *Mycobacterium tuberculosis* complex cell having an inactivated recA function, which may be used to generate an immune response in the treatment of various disorders. See Colston, col. 6, lines 34-37 and 41-48. Persistence of the live mycobacterium in the host is necessary for the vaccine composition to work. See Colston, col.15, line 63 to col. 16, line 2: "Our results unexpectedly show that RecA does not contribute to the establishment and maintenance of infection in *M. bovis* BCG or *M. tuberculosis*. This is an important finding since persistence of BCG following vaccination is thought to be a significant contributory factor to its immunogenicity; a mutant BCG which is rapidly eliminated would not be an effective vaccine" (emphasis added); see also, Colston, col. 2, lines 45-59.

Colston's RecA mycobacterial complex cells may have endogenous antigens that are cross-reactive with *M. tuberculosis* (see Colston, col. 3, lines 26-27), or may be genetically modified to comprise a gene encoding a non-mycobacterial or foreign polypeptide antigen, wherein expression of such an antigen allows the generation of an immune response against the foreign antigen in a vaccinated individual. See Colston, col. 4, lines 51-57. Suitable foreign antigens are disclosed to include viral, protozoal, tumour cell, bacterial and fungal antigens including, e.g., tetanus and diphtheria toxins. See Colston, col. 4, line 65 to col. 5, line 5.

2. Summary of the Examiner's Reasons for Rejection

The Examiner asserts that Baker and Colston are analogous art, and points to Baker's disclosure that the tryptanthrin compound can be administered with an adjuvant or in combination with another agent used to treat mycobacterial infections, and that antigens, such as BCG, are used in a vaccine against tuberculosis. Colston is cited as disclosing an "antigen delivery system" for treating diseases such as pathogenic infections ameliorated by an immune response against an antigen, as well as suitable antigens, including antigens from the tetanus and diphtheria toxins.

The Examiner acknowledges that Baker fails to disclose combination of the tryptanthrin compound and an antigen as disclosed in claim 14. Nevertheless, the Examiner takes the position that the claims are *prima facie* obvious because one of skill in the art would allegedly have been motivated to combine Baker's tryptanthrin compound with a composition comprising antigens associated with tetanus or diphtheria, as allegedly disclosed by Colston.

The Examiner cites *In re Kerkhoven* for the proposition that "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

3. Response to the Examiner's Reasons for Rejection

a. There is neither a motivation to combine nor a reasonable expectation of success based on the disclosures of Baker and Colston

Baker's tryptanthrin compounds are disclosed as antibacterial agents, useful for treating bacterial infections and for killing mycobacteria in particular. See Baker, col. 1, lines 7-14: "The

present invention relates to new indolo[2,1-b]quinazoline-6,12-dione derivatives which are useful in killing mycobacteria...." (emphasis added).

As discussed above, Colston's vaccine compositions contain live mycobacterium, and persistence of the live mycobacterium cell in the host without causing a progressive infection is necessary for their vaccine compositions to work. See Colston, col. 15, line 63 to col. 16, line 2. The use of Colston's composition as an "antigen delivery system" to confer immunity to a foreign antigen is described in the context of a genetically modified *M. tuberculosis* complex cell that *expresses* the foreign antigen. See Colston at col. 4, lines 51-60. Thus, Colston's compositions comprising foreign antigens, such as the tetanus or diphtheria antigens suggested by the Examiner, also contain live mycobacterium.

The combination relied upon by the Examiner to establish a *prima facie* case of obviousness thus requires mixing a vaccine composition that requires a live mycobacterium for its effectiveness with a tryptanthrin compound that is disclosed to kill mycobacteria. The Office has failed to provide a rationale sufficient to motivate one of ordinary skill in the art to combine the disclosures of Baker and Colston in view of this fundamental incompatibility between the cited references.

One of ordinary skill in the art would have reasonably expected Baker's anti-mycobacterial compounds to inactivate Colston's mycobacterium-dependent vaccine composition if the two were mixed together, rendering the composition ineffective. Thus, one of ordinary skill would have had neither a motivation to combine Baker's compounds with Colston's vaccine, nor a reasonable expectation that the combination would be effective. Baker's disclosure that its compounds are useful

to kill mycobacteria provides a clear, if implicit, teaching away from mixing it with Colston's vaccine compositions, which requires a live mycobacterium to be effective.

As discussed above, the 'adjuvants' disclosed by Baker are conventional pharmaceutical excipients, such as wetting agents, emulsifying agents, etc. Baker neither discloses nor otherwise suggests that these 'adjuvants' include vaccine adjuvants. In addition, the claims do not require combining a tryptanthrin compound with an adjuvant, but rather relate to a tryptanthrin compound acting as an adjuvant in the context of the claimed immunogenic composition. Even if Baker's 'adjuvants' could be construed to include vaccine adjuvants, the Examiner has failed to identify any guidance provided by Baker, alone or in combination with Colston, that would lead one of skill in the art to reasonably conclude that the tryptanthrin compounds *themselves* are capable of acting as adjuvants.

Moreover, Colston neither discloses nor otherwise suggests that the mycobacterium in their vaccine compositions can be replaced by a different adjuvant, and doing so would change the principle of operation of Colston's invention, which relies on the ability of mutated *M. tuberculosis* cells to survive for prolonged periods of time in a subject without causing progressive infection. See Colston at col. 3, lines 56-62. MPEP 2143.01(V) ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.")

b. Combination with Baker's compounds would render Colston's compositions unsuitable for their intended purpose

As discussed above, Colston's compositions require that a live mycobacterium persists in the treated subject to effectively generate an immune response to an antigen. A person of skill in

the art would have expected combining such mycobacterium-dependent compositions with the anti-mycobacterial compounds of Baker to kill the mycobacterium, inactivating the vaccine. Because the combination of Baker's compounds with the vaccine composition of Colston would be expected to render the vaccine unsuitable for its intended purpose, combining these references in an obviousness rejection is improper. See MPEP 2143.01(V) ("The proposed modification cannot render the prior art unsatisfactory for its intended purpose.")

With regard to the Examiner's assertion that these arguments are unpersuasive because the Appellants are allegedly "arguing against their own claimed invention" (see Office action at page 8), Appellants note that this is simply incorrect. The claimed compositions do not include a live mycobacterium cell, and such a cell is not required to provide an enhanced immune response to the antigen in the claimed compositions because the tryptanthrin compound itself functions as an adjuvant. Because the person of ordinary skill would not have had motivation to combine Baker's compounds with Colston's vaccine, or a reasonable expectation of success when doing so, the cited references do not support a *prima facie* case of obviousness.

c. One of skill in the art would have no motivation to practice the invention as claimed

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP § 2142.

The claims on appeal require that a tryptanthrin compound adjuvant and an antigen be mixed into a single, immunogenic composition. While Baker generally discloses that their compounds can be

administered in combination with another agent used to treat mycobacterial infections, exemplified by antibacterial agents, the cited portion of Baker does not disclose or suggest that the other agent be mixed with Baker's compound, or that the other active agent could be an antigen or vaccine. The only mention of vaccines or antigens in Baker is a brief discussion in the Background section of the limitations of the bacilli Calmette-Guerin (BCG) vaccine. See Baker, col. 1, lines 63-67.

No real reason has been provided why one of skill in the art would physically combine the compounds of Baker with the vaccine compositions of Colston into a single composition, and no advantage of mixing them together has been identified. The justification for physically combining them rests largely on *In re Kerkhoven*, where the Court noted that the combination required "no more than the mixing together of two conventional spray-dried detergents."

The antibacterial compounds of Baker and the vaccine compositions of Colston operate by different mechanisms and target different patient populations, vaccines being primarily preventive while small molecule agents are ordinarily used as a treatment. The two categories are well known to require different formulations and different routes and schedules of administration. In view of this, one of ordinary skill would not have been motivated to mix them together without some expected advantage. Those skilled in the art would not consider mixing an antibacterial agent and a vaccine composition together to be comparable to mixing the detergents in *Kerkhoven*.

In the instant case, the cited art fails to disclose or otherwise suggest that the compounds of Baker have adjuvant activity or should be combined with immunogenic compositions, or that the *M. tuberculosis* cells in Colston's compositions are replaceable by a different adjuvant. Thus, the cited art, alone or in combination, provides no guidance that would lead one of skill in the art to conclude that physically combining a compound of Baker with a vaccine composition of Colston would be

reasonably likely to provide an enhanced immune response to an antigen. Moreover, even if a compound of Baker was for some reason physically admixed with a vaccine composition, nothing in the cited art would lead one of skill in the art to conclude that the tryptanthrin compound would *necessarily* be present in an amount effective to promote an enhanced immune response to an antigen, as required by the claims.

d. The Office has improperly disregarded evidence teaching away from the proposed combination of Baker and Colston

The Examiner rejects as unpersuasive Appellants' arguments that because drug interactions are common, one of skill in the art would not routinely combine different classes of agents, such as antibiotics and vaccines, merely because they are generally used in the treatment and/or prophylaxis of the same disorder. In support of the Appellant's position that one of skill in the art would be concerned about drug interactions for the proposed combination of Baker's compounds and Colston's vaccine compositions, the Appellants submitted information from Medline Plus®, providing evidence that patients receiving the BCG vaccine are specifically cautioned to advise their physician of any other medications they are taking, in particular antibiotics. See Medline Plus® Drug Information:Baccillus Calmette-Guerin (BCG) Vaccine, at page 1 (submitted as Exhibit A with response filed 25 July 2008).

While admitting that drug interactions are a "general concern for anyone in the medical field" the Examiner improperly disregards this factor in the obviousness analysis because "it would apply to any drug combination." Appellants submit that such recognized interactions are *precisely* the kind of issue a person of ordinary skill would *necessarily* consider before mixing a vaccine with an antibiotic. The Examiner's argument that the combination could be administered once, followed by separate administration of the antibiotic, since the claims use the open transitional language

'comprising' misses the point: there is no reason to mix them together for even one administration, and many reasons *not* to.

The Examiner rejects as unpersuasive arguments that antibiotic compounds and vaccines act by vastly different mechanisms and are not ordinarily combined. The Examiner states that "there are many combination therapies in the medical field that work via different or multiple mechanisms of action. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating pathogenic mycobacterial infections by administering tryptanthrin with an adjuvant because of the therapeutically additive effect of combining two known active agents for the same purpose." However, the Examiner has provided no examples or evidence to suggest that one of ordinary skill would consider it normal or reasonable to combine an antibacterial agent with a vaccine.

The Examiner has disregarded the reference to Woo et al. (*Clinical Diagnostic Laboratory Immunol.* (1999), 832-37) provided by the Appellants suggesting that co-administering a vaccine and an antibiotic tends to reduce their effectiveness. See Woo et al. at, e.g., Abstract (submitted as Exhibit B with response filed 25 July 2008). The Examiner states that "the reference does not state that the combination of vaccines and antibiotics will not work, but that the combination will be less effective." The acknowledgement that the combination would be expected to be less effective contradicts the position that one of skill in the art would have been motivated to combine the agents to provide 'additive effects'. The Examiner's reliance on *Kerkhoven* appears misplaced, as *Kerkhoven* provides no reason to mix a vaccine with an antibacterial agent where the art suggests that making such a combination will generally reduce the effectiveness of the vaccine, which distinguishes the instant situation from *Kerkhoven's* facts. Moreover, in the instant case, the *particular* anti-mycobacterial

compounds of Baker would be expected to inactivate the *particular* mycobacterium-dependent vaccine of Colston, further distinguishing the instant situation from *Kerkhoven*.

Even if the cited references could be considered to suggest concurrent *use* of the tryptanthrin compounds with a vaccine, which the Appellants do not concede, that does not disclose, suggest or require mixing them into a single composition as required to support a determination of obviousness. The absence of *any* recognized advantage provided by the combination, in conjunction with the Examiner's admission that the art provides a reason to expect the combination of an antibacterial agent and a vaccine to be less active than the separate treatments, rebuts any conclusion that it would have been obvious to combine the teachings of the cited references.

Post-*KSR*, the Office still requires a reason to combine reference teachings. In this case, none has been provided, while the record shows that a person of ordinary skill had several reasons not to do so. These facts do not support a *prima facie* case of obviousness, because the person of ordinary skill had no reason to make the combination proposed by the Examiner, and every reason to doubt that such a combination would be effective.

B. The Examiner has improperly disregarded express claim limitations

1. Summary of the Examiner's Reasons for Rejection

The Examiner states on page 3 of the Office action that the claim limitation "for enhancing an immune response to the antigen" in claim 12 is considered part of the preamble or is merely a recitation of intended use, and will be afforded little patentable weight since the claims are drawn to compositions. Appellants note that the limitation in claim 12 actually recites that the tryptanthrin compound adjuvant is present "in an amount effective to provide an enhanced immune response to the antigen...."

The Examiner also affords little patentable weight to the limitations that the composition be "immunogenic" and "providing an enhanced immune response to the antigen than provided without the tryptanthrin compound adjuvant" in claim 12, and that the tryptanthrin compound "enhances an immune response to the antigen and the immune response is the cellular production of one or more cytokines" in claim 15, because the Examiner asserts that these claim limitations recite inherent properties.

2. Response to the Examiner's Reasons for Rejection

The Examiner has improperly disregarded express claim limitations in claims 12 and 15 that distinguish the claimed invention *as a whole* from the cited art. The recitation in the preamble of claim 12 that the compositions are *immunogenic* limits the structure of the claimed compositions to those wherein the tryptanthrin compound adjuvant is present in an amount effective to provide an enhanced immune response to the antigen, and gives meaning to the express limitations in the body of claims 12 and 15 related to the enhanced immune response, which have also been improperly disregarded by the Examiner. Accordingly, the recitation that the composition is "immunogenic" in the claim preamble should be afforded patentable weight in assessing the differences between the cited documents and the claimed invention as a whole. "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). MPEP § 2111.01.

Regardless of the patentable weight afforded to the term "immunogenic" in the preamble of claim 12, the Examiner has improperly ignored the functional limitation in claim 12 (and the

claims which depend thereon) requiring that the adjuvant be present in "an amount effective to provide an enhanced immune response to the antigen," as well as the limitation in claim 15 requiring that "the immune response is the cellular production of one or more cytokines." These limitations clearly distinguish the claimed invention from the cited art, which does not recognize that tryptanthrin compounds can function as adjuvants, and the Examiner has pointed to nothing in the cited art that teaches or otherwise suggests these features of the instant invention.

The Examiner asserts that these claim limitations recite inherent properties, and are not entitled to patentable weight, because "[p]roducts of identical chemical composition can not have mutual [sic] exclusive properties. Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present." (Office Action, page 4.) The Examiner further asserts that "since the cited prior art discloses all components in the prior art, the limitations drawn to the properties of the composition is inherent." (Office Action, page 7.)

While individual components of the present invention (i.e., tryptanthrin compounds, antigens) may have been *separately* known in the prior art, that is not the Appellants invention. "In determining the differences between the prior art and the claims, the question under **35 U.S.C. 103** is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); MPEP 2141.02(I).

The Examiner has acknowledged that the claimed immunogenic compositions, which include both an antigen and a tryptanthrin compound adjuvant in an amount effective to provide an

enhanced immune response to the antigen, were not known in the prior art, and the properties of unknown compositions (inherent or otherwise) cannot be considered to have been present in the prior art. "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993); MPEP 2141.02(V). Clearly, the allegedly 'inherent' properties of *hypothetical* compositions cannot properly be relied upon to establish obviousness.

The Office has failed to meet its burden of proof in establishing a basis in fact or technical reasoning to support the determination that the claimed immunogenic compositions, and in particular the limitation that the tryptanthrin compound adjuvant is present in an amount effective to provide an enhanced immune response to the antigen, would *necessarily* be present in the proposed combination of Baker's compounds and Colston's mycobacterium-dependent vaccine compositions.

C. Evidence of unexpected results rebuts any *prima facie* case of obviousness

Because the Office has failed to establish a *prima facie* case of obviousness, the Appellants have no burden to submit rebuttal evidence. Nevertheless, the record provides a significant amount of evidence rebutting a conclusion of obviousness.

The specification demonstrates that the tryptanthrin compounds produce an unexpected immune-stimulating response in the claimed compositions. See Specification at Table 1. The Declaration of Nicholas Valiante, Jr. submitted with the response filed 31 October 2007 (hereinafter "Valiante Declaration") discloses that tryptanthrin compounds unexpectedly stimulate production of TNF-alpha, suggesting these compounds are useful as adjuvants to potentiate an immune response. See Valiante Declaration at paragraphs 5-6. These effects could not have been expected based on the cited art, which discloses only antibacterial activity for the tryptanthrin compounds.

The Examiner has rejected this evidence, saying, "Examiner does not view this as unexpected properties since tryptanthrin is a known compound." Appellants note that the inherent properties of a known compound are not themselves known, and cannot be relied upon to support a conclusion of obviousness. MPEP § 2141.02(V). The inherent properties of the tryptanthrin compounds that are the subject of the present invention—their ability to promote an enhanced immune response to an antigen—would not have been expected.

The determination of obviousness or nonobviousness must be made in view of all of the evidence of record. When rebuttal evidence is presented for an alleged *prima facie* case of obviousness, the Examiner must consider all of the evidence before arriving at an ultimate conclusion. MPEP 2145. Because the application and the Valiante Declaration provide evidence of unexpected effects, a conclusion that the claimed invention would have been obvious is rebutted.

D. Conclusion

The present invention provides an immunogenic pharmaceutical composition comprising an antigen and a tryptanthrin compound adjuvant in an amount effective to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant. The cited art fails to provide a *prima facie* case of obviousness, and few of Appellants' arguments have been addressed on the record. Appellants respectfully request reversal and allowance of claims 12-17 and 19.

The combination of Baker's compounds with Colston's mycobacterium-dependent vaccines would not be expected to work because of the anti-mycobacterial activity of Baker's compounds. That alone is sufficient to destroy the alleged *prima facie* case of obviousness. Appellants have shown that mixing pharmaceutical agents raises concerns about drug interactions,

and have provided evidence that combining an antibiotic with a vaccine is expected to reduce the vaccine's effectiveness and is not customary in the art. All of this evidence stands unrebutted. For pharmaceutical arts generally, and for vaccines in particular, these facts distinguish mixing agents together in the relevant art from mixing the detergents in *Kerkhoven*. Finally, the immune enhancing activity of the claimed compositions provides an unexpected result, which was neither disclosed nor suggested by the cited art, and is sufficient to rebut any conclusion of obviousness. Even if a *prima facie* case for obviousness were established, it would be overcome by the unrebutted evidence favoring a conclusion of nonobviousness.

VIII. CLAIMS APPENDIX

An appendix containing a copy of the claims as currently pending is attached hereto as Appendix A.

IX. EVIDENCE APPENDIX

An appendix containing the following documents already of record in this case is attached hereto as Appendix B:

1. Baker et al. (U.S. Patent 5,441,955)
2. Colston et al. (U.S. Patent 7,122,195)
3. Declaration of Nicholas Valiante, Jr. under 37 C.F.R. § 1.132, submitted with response filed 31 October 2007.
4. Medline Plus®, Drug Information: Baccillus Calmette-Guerin (BCG) Vaccine, submitted as Exhibit A with response filed on 25 July 2008.

5. Woo et al., *Clinical Diagnostic Laboratory Immunol.* (1999), 6(6):832-37, submitted as Exhibit B with response filed on 25 July 2008.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings, therefore no Appendix is included.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: January 28, 2010

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APPENDIX A

Complete Listing of the Claims, including Claims Involved in the Appeal of Application Serial 10/762,873:

1. (withdrawn): A method of enhancing an immune response in a subject to an antigen, the method comprising administering to a subject an immunogenic pharmaceutical composition comprising the antigen and a tryptanthrin compound adjuvant in an amount effect to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant.

2. (withdrawn): The method of claim 1, wherein the antigen is derived from a bacterial, parasitic, viral, or fungal pathogen.

3. (withdrawn): The method of claim 2 wherein the bacterial pathogen is selected from the group consisting of diphtheria, staphylococcus, cholera, tuberculosis, tetanus, streptococcus pneumoniae, streptococcus agalacitiae, streptococcus pyogenes, pertussis, Neisseria meningitis, Neisseria gonorrheae, chlamydia, Helicobacter pylori, and Hemophilius influenza type B.

4. (withdrawn): The method of claim 2 wherein the viral pathogen is selected from the group consisting of viral meningitis, rhinovirus, influenza, respiratory syncytial virus, parainfluenza virus, rotavirus, tick borne encephalitis virus, coronaviridae, rhabodoviridiae, VZV, EBV, CMV, HIV, HPV, HSV, HAV, HBV, HCV, and SARS.

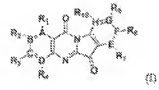
5. (withdrawn): The method of claim 2 wherein the parasitic pathogen is selected from the group consisting of Plasmodium falciparum, Plasmodium ovate, Plasmodium malariae, and P. vivax.

6. (withdrawn): The method of claim 2, wherein the antigen is associated with a disease selected from the group consisting of BCG, cholera, plague, typhoid, hepatitis B infection,

influenza, inactivated polio, rabies, measles, mumps, rubella, oral polio, yellow fever, tetanus, diphtheria, hemophilus influenzae b, meningococcus infection, tick borne encephalitis, SARS, HCV, HIV, and pneumococcus infection.

7. (withdrawn): The method of claim 1 wherein the immune response is the cellular production of one or more cytokines.

8. (withdrawn): The method of claim 1 wherein the tryptanthrin compound is a compound of Formula (I):



(I)

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen, or A and B and/or C and D can he taken together to be nitrogen or sulfur; R_1, R_2, R_3, R_4, R_8, and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, cycloalkyl, heterocyclyl, alkylheterocyclyl, substituted heterocyclyl, substituted alkenyl, amino, (substituted alkyl)(alkyl)amino, imino, halololoweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, alkylsulfonyl, N-alkylsulfonamide, arylalkyl, arylalkylaryl, arylaryl, aryloxy, arylamino, acylamino, acyloxyamino, alkylaminoacylamino, alkylaminosulfonylamino, alkylamino, alkenylamino, dialkylamino, alkoxyalkylamino, alkoxyalkylheterocyclyl, mercaptoalkoxyalkyl, cyano, formyl, $-COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and $-CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues; or R_2 and R_3 taken together form a six membered aromatic ring;

R_7 and R_9 are independently selected from hydrogen, halogen, loweralkyl, halololoweralkyl, cycloalkyl, heterocyclyl, substituted heterocyclyl or heterocyclylalkyl; and

R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are absent when the ring atom to which they would otherwise be bonded is sulfur or double-bonded nitrogen; or

a pharmaceutically acceptable salt,

provided that R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are not all hydrogen when A, B, C, D, E, F, and H are carbon.

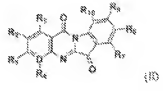
9. (withdrawn): The method of claim 8,

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen;

R_1, R_2, R_3, R_4, R_8 and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, substituted alkenyl, (substituted alkyl)(alkyl)amino, haloloweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, N-alkylsulfonamide, cyano, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues.

10. (withdrawn): The method of claim 1 wherein the tryptanthrin compound is a compound of Formula (II):



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or halologweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, halologweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$ wherein R_{11} is loweralkyl, or $-CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

11. (withdrawn): The method of claim 1, wherein the tryptanthrin compound is selected from the group consisting of:

8-nitroindolo[2,1-b]quinazoline-6,12-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-chloro-8-iodoindolo- [2,1-b]quinazoline-6,12-dionc,

2,4-dibromo-l-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

3-[(2-hydroxyethyl)thio]-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a] indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11 dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

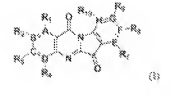
12. (previously presented): An immunogenic pharmaceutical composition comprising an antigen and a tryptanthrin compound adjuvant in an amount effective to provide an enhanced immune response to the antigen relative to the response provided without the tryptanthrin compound adjuvant.

13. (original): The composition of claim 12, further comprising an aqueous carrier.

14. (previously presented): The composition of claim 12, wherein the antigen is associated with a disease selected from the group consisting of cholera, plague, typhoid, hepatitis B infection, influenza, inactivated polio, rabies, measles, mumps, rubella, oral polio, yellow fever, tetanus, diphtheria, hemophilus influenzae b, meningococcus infection, tick borne encephalitis, SARS, HCV, HIV, and pneumococcus infection.

15. (previously presented): The composition of claim 12, wherein the tryptanthrin compound enhances an immune response to the antigen and the immune response is the cellular production of one or more cytokines.

16. (original): The composition of claim 12, wherein the tryptanthrin compound is a compound of Formula I:



wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen, or A and B and/or C and D can be taken together to be nitrogen or sulfur;

R_1, R_2, R_3, R_4, R_8, and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, cycloalkyl, heterocyclyl, alkylheterocyclyl, substituted heterocyclyl, substituted alkenyl, amino, (substituted alkyl)(alkyl)amino, imino, halololoweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, alkylsulfonyl, N-alkylsulfonamide, arylalkyl, arylalkylaryl, arylaryl, aryloxy, arylamino, acylamino, acyloxyamino, alkylaminoacylamino, alkylaminosulfonylamino, alkylamino, alkenylamino, dialkylamino, alkoxyalkylamino, alkoxyalkylheterocyclyl, mercaptoalkoxyalkyl, cyano, formyl, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues; or R_2 and R_3 taken together form a six membered aromatic ring;

R_7 and R_9 are independently selected from hydrogen, halogen, loweralkyl, halololoweralkyl, cycloalkyl, heterocyclyl, substituted heterocyclyl or heterocyclylalkyl; and

R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are absent when the ring atom to which they would otherwise be bonded is sulfur or double-bonded nitrogen; or

a pharmaceutically acceptable salt thereof,

provided that R_1, R_2, R_3, R_4, R_7, R_8, R_9, and R_{10} are not all hydrogen when A, B, C, D, E, F, and H are carbon.

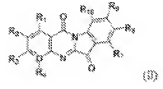
17. (original): The composition of claim 16,

wherein

A, B, C, D, E, F, G, and H are independently selected from carbon and nitrogen;

R_1, R_2, R_3, R_4, R_8 and R_{10} are independently selected from the group consisting of hydrogen, halogen, loweralkyl, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, substituted alkenyl, (substituted alkyl)(alkyl)amino, halololoweralkyl, hydroxy, alkoxy, substituted alkoxy, hydroxyalkylthio, nitro, N-alkylsulfonamide, cyano, -$COOR_{11}$ wherein R_{11} is hydrogen, loweralkyl, aryl, heterocyclyl, monosaccharide or disaccharide, and -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently selected from hydrogen, loweralkyl, aryl, heterocyclyl, saccharide, peptide and amino acid residues.

18. (withdrawn): The composition of claim 12, wherein the tryptanthrin compound is a compound of Formula II:



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or halololoweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, halololoweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$ wherein R_{11} is loweralkyl, or -$CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

19. (original): The composition of claim 12, wherein the tryptanthrin compound is selected from the group consisting of

8-nitroindolo[2,1-b]quinazoline-6,l-2-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-chloro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6, 12-dione,

3-[(2-hydroxyethyl)thio]-8-[(tri fluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

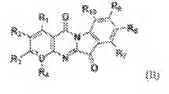
6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

20. (withdrawn): A method of immunotherapy for the treatment of cancer, the method comprising administering to a subject an immunostimulatory effective amount of a tryptanthrin derivative.

21. (withdrawn): The method of claim 20, wherein the tryptanthrin derivative is a compound of Formula II:



(II)

wherein

D is carbon or nitrogen, and R_4 is absent when D is N;

R_1 is hydrogen, halogen, or loweralkyl;

R_2 is hydrogen or halogen;

R_3 is hydrogen, halogen, heterocyclyl, substituted heterocyclyl, (substituted alkyl)(alkyl)amino, or hydroxyalkylthio;

R_4 is hydrogen, halogen, alkoxy, substituted alkoxy, or hydroxy;

R_7 is hydrogen or halololoweralkyl;

R_8 is hydrogen, halogen, substituted alkoxy, halololoweralkyl, nitro, N-alkylsulfonamide, substituted alkenyl, substituted alkyl, $COOR_{11}$, wherein R_{11} is loweralkyl, or $-CONR_{12}R_{13}$ wherein R_{12} and R_{13} are independently hydrogen or loweralkyl;

R_9 is hydrogen; and

R_{10} is hydrogen, halogen, or loweralkyl;

or a pharmaceutically acceptable salt thereof.

22. (withdrawn): The method of claim 20, wherein the tryptanthrin derivative is selected from the group consisting of

8-nitroindolo[2,1-b]quinazoline-6,12-dione,

3,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

10-fluoroindolo[2,1-b]quinazoline-6,12-dione,

1,8-difluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-l-methylindolo[2,1-b]quinazoline-6,12-dione,

8,10-difluoroindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-l-fluoro-8-iodoindolo[2,l-b]quinazoline-6,12-dione,

2,4-dibromo-l-chloro-8-iodoindolo[2,1-b]quinazoline-6,12-dione,

2,4-dibromo-1-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-2-iodoindolo[2,1-b]quinazoline-6,12-dione,

8-chloro-3-fluoroindolo[2,1-b]quinazoline-6,12-dione,

8-fluoro-4-hydroxyindolo[2,1-b]quinazoline-6,12-dione,

N-ethyl-4-(methyloxy)-6,12-dioxo-6,12-dihydroindolo[2,1-b]quinazoline-8-carboxamide,

3-fluoro-8-[(trifluoromethyl)oxy]indolo[2, 1-b]quinazoline-6,12-dione,

3-[(2-hydroxycthyl)thio]-8-[(trifluoromethyl)oxy]indolo[2,1-b]quinazoline-6,12-dione,

pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-fluoropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-bromopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-chloropyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

9-iodopyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

ethyl 5,11-dioxo-511-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-carboxylate,

N-octyl-5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indole-9-sulfonamide,

10-(trifluoromethyl)pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

(5E)-6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hex-5-enyl acetate,

6-(5,11-dioxo-5,11-dihydropyrido[2',3':4,5]pyrimido[1,2-a]indol-9-yl)hexyl dihydrogen phosphate, and

9-[(trifluoromethyl)oxy]pyrido[2',3':4,5]pyrimido[1,2-a]indole-5,11-dione,

or a pharmaceutically acceptable salt thereof.

23.-31. (canceled)

APPENDIX B

This appendix contains the following evidentiary material already of record:

1. Baker et al. (U.S. Patent 5,441,955)
2. Colston et al. (U.S. Patent 7,122,195)
3. Declaration of Nicholas Valiante, Jr. under 37 C.F.R. § 1.132, submitted with response filed 31 October 2007.
4. Medline Plus®, Drug Information: Baccillus Calmette-Guerin (BCG) Vaccine, submitted as Exhibit A with response filed on 25 July 2008.
5. Woo et al., *Clinical Diagnostic Laboratory Immunol.* (1999), 6(6):832-37, submitted as Exhibit B with response filed on 25 July 2008.